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14. ABSTRACT

The protocols for the 10 proposed prospective multicenter clinical trials have been completed, approved by individual participating organization internal review boards, have been submitted to HSRRB at USAMRMC and have undergone preliminary review. Changes in protocols have been made and protocols re-reviewed by internal review boards and we are awaiting formal HSRRB review and approval.
The JVN CDMP application has been deployed in VA VISN 1 network and deployed on Walter Read Army Medical Center ICDB. Currently working to integrate into CHCS II when deployed at WRAMC. JVN CDMP application not deployed at Tripler Army Medical Center as command decision was to discontinue studies pending deployment of CHCS II. The Hawaii project is now focused on deployment to 3 community health centers and is the subject of a BAA modification associated with this program.
CDMP development for new modules is being accomplished. Study management module completed.

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INTRODUCTION

The major goals of this continuing project are the establishment of a telemedicine system for comprehensive diabetes management and the assessment of diabetic retinopathy that provides increased access for diabetic patients to appropriate care, that centralizes the patients in the care process, that empowers the patient to better manage their disease, that can be performed in a cost effective manner, and that maintains the high standard of care required for the appropriate management of diabetic patients.

The aim of this continuation will be to perform the appropriate clinical validation, cost efficiency, and risk benefit studies associated with the use of the recently developed Comprehensive Diabetes Management Program (CDMP) and the Joslin Vision Network (JVN) Eye Health Care Program that is now a module of the CDMP. This proposal will also have a secondary focus on continuing technology centric research associated with the development of new modules for the CDMP, and development and validation of computer algorithms designed to automate detection of retinal lesions developed during the course of retinopathy development.

The need for diabetes disease management is driven by the knowledge that diabetes is not currently curable, but it is treatable, and its complications are preventable. The primary goal of treatment is to manage diabetes to live a healthy life. In general, the traditional physician-centered, episodic, acute-care model is not designed to care for large numbers of diabetic patients (2,200 new cases diagnosed every day in the US) and in order to meet this challenge the health care delivery system will need to be re-engineered. This can become a reality with the use of the CDMP developed under this collaborative effort.

BODY

Summarized below is the originally proposed Statement of Work (SOW) for reference:

1. Prospective multi center cost efficiency study performed using the JVN Telehealth Eye Care module
2. Prospective multi-center risk benefit study using the JVN Telehealth Eye Care module
3. JVN Telehealth CDMP program usability and impact on clinical workflow study
4. Prospective multi-center clinical outcomes efficacy and cost efficiency study using the JVN Telehealth Comprehensive Diabetes Management Program
5. Clinical validation of the Behavior Assessment Tool (BAT) developed for the JVN Telehealth CDMP application
6. Development and validation of Learning Level Assessment and Readiness to Learn tools for the JVN Telehealth CDMP application
7. Deployment of JVN Telehealth CDMP application in Tripler Army Medical Center and Honolulu VA in Hawaii
8. Deployment of JVN Telehealth CDMP application in VA VISN 1 network
9. Deployment of JVN Telehealth CDMP application into the Department of Defense TRICARE Online computer system
10. Establish a centralized JVN Telehealth clinical coordination center to facilitate the proposed multicenter clinical trials
11. Clinical validation of the JVN Eye Care computer algorithm for automation of detection of retinal lesions
12. Clinical validation study for the JVN developed retinal imaging device
13. Automation of the retinal image taking process using the JVN developed retinal imaging device
14. Migration of JVN Eye Care module to Microsoft .Net operating platform
15. Development of additional modules for the JVN Telehealth CDMP application to include an outcomes and reporting module, an education scheduling and tracking tool, a knowledge assessment tool, a nutrition module, a patient portal module, integration of wireless home monitoring devices, and a primary care practitioner module

Status Report for Research Projects Supported by the DoD Collaborative (SOW # 1 to #5)

The DoD collaborative has 8 research projects planned, to take place at 4 sites. These each entail testing some aspect of the Comprehensive Diabetes Management Program or its components, namely the Joslin Vision Network (JVN) or the Behavioral Assessment Tool (BAT). In addition, we are working with the American Institutes for Research (AIR) to

conduct a human factors study of the CDMP; there is a research component to this work involving "usability testing" and an Expert Review component. The projects are indicated by site in the following table:

Project	Joslin	Hawaii	WRAMC	VA Boston
An Assessment of the Test-Retest **Reliability** of the CDMP BAT	√	√	√	√
An Assessment of the **Validity** of the CDMP BAT	√	√	√	
Digital Photography and Group Discussion as a Means of Affecting Dietary Change among People with Type 2 Diabetes: Feasibility Project	√			
CDMP: Usability and Impact of the Workflow on Diabetes Care Specialists and on their Process and Quality Measures			√	
Prospective Multi-center Clinical Outcomes Efficacy and Cost Efficiency Study Using the JVN CDMP	√	√	√	
Prospective Multi-center Economic Analysis of the JVN Telehealth Eye Care Module			√	
Internet-based Diabetes Education and Case Management				√
Prospective Risk Benefit Analysis of the JVN Telehealth Eye Care Module				√
Additional Human Factors Study for the CDMP Application: Expert Review of the CDMP (second half)	NA	NA	NA	NA
Additional Human Factors Study for the CDMP Application: Usability Testing of the CDMP (first half)	√			

Notes: NA means not applicable. The Expert Review of the CDMP does not require recruiting subjects and is done by employees of AIR at their offices.

The remainder of this section summarizes the aims and provides a status report of each project.

An Assessment of the Test-Retest Reliability of the CDMP BAT. The BAT is a new, stand-alone screening questionnaire within the CDMP that contains questions about psychosocial factors, nutrition, physical activity, alcohol and tobacco use, medications, general health, self-monitoring of blood glucose and economic factors. Since the BAT is a new instrument, it is necessary to test its consistency across repeated administrations, i.e., test-retest reliability. The objectives of this study are, first, to determine the test-retest reliability of the BAT and, second, to examine whether the BAT's test-retest reliability is invariant across social-demographic groups, health groups, and sites participating in the study. This is a multi-site observational study with two measurements per study subject taking place 2 to 4 weeks apart. The study protocol will involve recruiting 42 English-speaking individuals from each site who are 20+ years of age and have type 1 or 2 diabetes. Eligible and interested participants will asked to complete a test to assess their executive/cognitive function, questions about their social-demographics, and the BAT. For the data analyses, we will calculate the correlation between the two administrations of the BAT. Additionally, we will calculate mean item scores and mean summary scores for the sub-sections of the BAT and then use one-way analysis of variance to examine differences in the means among social-demographic groups, among health groups (e.g., differentiated by A1c, BMI, cognitive functioning, etc.), and between the two administrations of the BAT for each social-demographic group and health group. Lastly, we will combine data from all of the study sites and replicate the correlational analyses.

Status: This study has been approved by the Joslin IRB and is awaiting approval from the HSRRB. It is under review at the VA Boston and will be submitted to the IRB at WRAMC shortly.

An Assessment of the Validity of the CDMP BAT. Similar to the reliability study (see above), this project is concerned with the measurement properties of the BAT; however, this study focuses on its criterion, concurrent, and predictive validity. Concurrent validity is the correlation between a measure and an external criterion at the same point in time. Predictive validity is the correlation between a measure and an external future criterion. This is a multi-site observational study with three measurements per study participant taking place 6 months apart. We expect to recruit 75 participants from each site. Study participants will be asked to complete the BAT, provide anthropometrics, complete questionnaires and logs/diaries

containing background and criterion questions. We will validate the BAT against the following validated instruments and/or methods: seven-day food diaries, seven-day physical activity diaries, certain physical measures, medical records, the Short Form Health Survey Questionnaire (SF-36), an abbreviated, validated version of the Center for Epidemiologic Studies – Depression (CES-D) scale, the Diabetes Social Support Questionnaire (DSSQ), the Summary of Diabetes Self-care Activities Questionnaire – Revised (SDSCA-Revised), the Fagerstrom Tolerance Questionnaire (FTQ), the CAGE instrument, and several questions used in clinical assessment and/or other surveys but that are not part of scales. For the analysis of criterion and concurrent validity, we will correlate scores from sub-sections of the BAT with the scores from corresponding questionnaires, logs, anthropometrics, and medical record data obtained at approximately the same time. Predictive validity will be evaluated by correlational analysis and regressing (in multiple regression models) health factors (i.e., A1c, BMI, adherence to recommended foot and eye exams, number of days of sick leave, number of hospitalizations, number of hospital days, etc.) on scores from the sub-sections of the BAT and (where appropriate) responses to individual BAT questions completed at previous observations.

Status: This study has been approved by the Joslin IRB and is awaiting approval from the HSRRB. It will be submitted to the IRB at WRAMC shortly.

Digital Photography and Group Discussion as a Means of Affecting Dietary Change among People with Type 2 Diabetes: Feasibility Project. The purpose of this study is to test the feasibility of a new approach to diabetes nutrition care involving digital food photography and facilitated group discussions of the digital photographs. The overall hypothesis regarding this new approach is that, by photographing all meals and snacks (i.e., keeping 'photo journals') and participating in discussions about the photographs with peers and a nutritionist, people with diabetes will become aware of their behaviors and develop concrete strategies to meet nutritional recommendations. The study design is that of a randomized controlled trial with two groups: one group will receive standard diabetes nutrition care; the other group will receive the new approach to diabetes nutrition care involving digital photography of meals and group discussion of the photographs (treatment group). The required sample size is 36 (18 in each group). All subjects complete study questionnaires and a blood draw before the digital photography and discussion sessions begin and at least 1 month (or more) after the digital photography discussion sessions end. Baseline data will be evaluated using descriptive analyses. The hypotheses will be evaluated using standard comparison tests, such as two-sample t tests and ANOVA.

Status: Initially this study was supported by a Mass Lions grant to Sven Bursell and by an NIH grant to the GCRC at Joslin. With this funding, we drafted a protocol, obtained approval from the Joslin IRB, enrolled 30 study participants, and completed a discussion session for 5 study participants in the treatment group. As of late December, however, we obtained additional funding support from the DoD Cooperative Agreement. This was necessary in order to pay for additional digital cameras, and a part-time research assistant, among other things. Since this change in sponsorship, we learned that the DoD requires that all studies it funds obtain approval from its HSRRB. Thus, we have suspended the study until the HSRRB completes its review.

CDMP: Usability and Impact of the Workflow on Diabetes Care Specialists and on their Process and Quality Measures. This project will examine the usability and impact on clinical workflow of the CDMP. Specifically, we will: a) examine the Diabetes Healthe*C*ard data (which documents the process and quality measures of the Diabetes Quality Improvement Program (DQIP)) of selected diabetes health care providers in the Walter Reed Army Health Care System (WRHCS); b) administer questionnaires regarding aspects of the diabetes care system before and after adoption of the CDMP; c) evaluate the use of the CDMP by observing the interactions of these care providers with standardized patients (i.e., actors who have been trained to provide a realistic initial or follow-up history for a simulated patent); and d) use structured focus group discussions with the providers lead by a trained, experienced facilitator. Health care providers selected for this study will be the Nurse Practitioners (NPs) of the Diabetes Institute of the WRHCS, all of whom have participated in developing the CDMP. The data will be analyzed qualitatively and quantitatively and summarized by descriptive statistics and graphical displays. We will analyze quality of performance, ease, speed, efficiency, cost effectiveness, accuracy and safety as a function of several design parameters. Where appropriate, we will use exploratory data analysis, paired and unpaired Student's *t* tests, chi-square and z tests for differences of proportions, analysis of variance, correlation, and regression methods. Qualitative data will be analyzed using nonparametric statistics and using transformations, ranks, or percentiles.

Status: This study has received approval from the IRB at WRAMC. The HSRRB has deferred review of it and granted us permission to proceed. Study participants have been enrolled and consented. Training in the use of the CDMP will take place in May/June.

Prospective Multi-center Clinical Outcomes Efficacy and Cost Efficiency Study Using the JVN CDMP. This study will determine the effectiveness, safety, and acceptance of the CDMP combined with a web-based blood glucose data monitoring and computer-assisted decision system (CADS). Specifically, it will determine whether use of the CDMP with CADs is associated with a) improvements in glycemic control, b) a decrease in the number hypoglycemic episodes and clinic visits, emergency room visits, hospitalizations, and hospital days for diabetes-related causes, c) a reduction in the development of microvascular complications of diabetic retinopathy and nephropathy or mitigation of the progression of these complications, d) improvement in lipid profiles, and f) improved quality of life for patients. We have planned an open, prospective, randomized clinical trial with 2 groups: 1 group will receive standard care, or no access to CDMP and CADS through their provider; the other group will receive CDMP and CADs through their provider. The trial will last for two years. The analysis will follow the intention-to-treat principle and patients who received the CDMP and CADS will be compared against participants who received standard care. We will examine group differences in baseline characteristics and outcomes using Student's *t* tests and Chi-Square tests. We will use repeated measures analyses to compare changes (e.g., treatment means or treatment regression curves) over the course of the study. The analyses will account for possible clustering effects.

Status: We have not drafted the protocol for this study yet. We are waiting for the completion of the usability studies and any modifications to the CDMP that may result from it. We are also applying for additional financial support.

Prospective Multi-center Economic Analysis of the JVN Telehealth Eye Care Module. *The purpose of this study is to compare the costs and cost-effectiveness of the JVN with conventional clinic-based eye examinations among a diabetic cohort receiving annual eye examinations. The research design is a randomized clinical trial that will provide prospective data for insertion into decision models. In turn, the decision models will generate the data to evaluate the cost-effectiveness of the JVN versus conventional clinic-based eye examinations. Consenting patients at sites of the Walter Reed Army Health Care System (WRHCS) with type 1 or type 2 diabetes mellitus and scheduled for eye examinations on an annual basis will be enrolled in the study and randomized to conventional clinic-based eye examinations or eye examinations performed by the JVN (plus an assessment of visual acuity). Subjects will be followed for one year. The study will track all costs that accrue over that year in the provision of care for both modalities, including labor, equipment, travel for the study subjects, and lost wages/productivity for study subjects, among others. Cost-effectiveness will be measured based on study subjects' compliance with the clinical eye examination and follow-up recommendations and diagnostic and treatment outcomes. We will a priori generate cost-effectiveness data based on diagnoses of diabetic retinopathy and macular edema. In a cost consequence analysis, we will consider other diagnostic outcomes and outcomes in aggregate. Additionally, we will impute cases of expected vision loss and, therefore, project differences in the number of cases of vision loss averted between modalities.*

Status: We have completed drafting the protocol for this study and are submitting it to the IRB at WRAMC.

Internet-based Diabetes Education and Case Management. Patients with diabetes and elevated HbA1c are at the greatest risk for diabetes-related complications. Care-management may be helpful in this situation, by providing direct contact between high-risk patients and the healthcare system. This study will examine the efficacy and cost-effectiveness of two methods of diabetes education and care management; one is the traditional model involving face-to-face encounters and telephone contact; the other is an Internet-based model. We will compare these interventions to a usual care control group that receives no education or care management but is provided with a notebook computer and Internet access. This study employs a randomized, prospective, parallel group design involving patients with diabetes mellitus. Primary outcome measures include clinical data (e.g. HbA1c, blood pressure, quality of life questionnaires) and secondary outcome measures include economic data (e.g. costs of case management, medication usage, and number(s) of ER visits/hospitalizations during the study period). We will study 150 participants with elevated HbA1c (8.5%). Over 12-months we will measure HbA1c, office BP, and scores on the Problem Areas in Diabetes (PAID) questionnaire. Participants receiving usual care will receive a notebook computer and Internet access. Those assigned to Internet-based care management will receive a notebook computer, Internet access and will interact with a care manager through a diabetes education and care management website. Those receiving traditional care management will interact with a care manager following a structured contact schedule. Both care management models will employ medication algorithms to improve glucose and BP control, with the secondary goal of also improving diabetes-related stress and depression. We will collect data on process measures and health care utilization in order to conduct exploratory analyses on the cost-effectiveness of these interventions.

Status: This study has received approval from the VA Boston IRB and an initial review from the HSRRB. We are now responding to the HSRRB's comments.

Prospective Risk Benefit Analysis of the JVN Telehealth Eye Care Module. We hypothesize that the JVN, supplemented with a non-invasive eye care assessment (hereafter referred to as *Technology Assisted Ophthalmic [TAO] examination*), can substitute for a complete eye exam with a dilated fundus evaluation by an eye care professional in patients with diabetes. To establish its validity, the JVN must be compared *prospectively* to a complete eye examination with dilated fundus evaluation, which is currently the standard-of-care. Such a comparison would also allow for an economic analysis of the JVN in its ability to accurately diagnose diabetic and non-diabetic eye diseases that require referral for eye care. To test this hypothesis we propose the following objectives: 1) To determine -- at baseline and prospectively over 2 years -- the accuracy and level of agreement of a TAO examination and a complete eye examination for (a) need for referral to an eye care professional for further evaluation, (b) level of diabetic retinopathy, and (c) other referable non-diabetic eye disease; and 2) To perform a cost minimization analysis comparing the TAO examination to the complete eye examination based on appropriate referral for follow-up eye care. We will study 500 patients with diabetes and at least one high-risk characteristic for the presence and/or progression of diabetic retinopathy using both a TAO examination and a complete eye examination, to determine at baseline the accuracy and level of agreement between the two modalities. High-risk characteristics include: current insulin use, longer duration of diabetes (>10 years), elevated A1c (>8%), renal disease (serum creatinine >1.5 mg/dl and/or albuminuria), and elevated blood pressure (systolic BP >160 mm Hg). We estimate that 40% of the initial patients will require early follow-up eye care based on findings of their baseline examination. Those patients whose initial diagnosis suggests no significant diabetic retinopathy and no non-diabetic eye diseases (approximately 300 patients) will be followed prospectively over a 2 year period with an annual TAO and complete eye exam to prospectively determine the accuracy and level of agreement. After the 2 year follow-up, we will perform a cost minimization analysis comparing the TAO examination to the complete eye examination based on need for referral for eye care.

Status: This study has received partial funding from the VA, in addition to the funding from the DoD collaborative. The funding will be available in the fall. In the meantime, we are submitting the protocol to the VA IRB and, once it is approved, we will submit it to the HSRRB.

Additional Human Factors Study for the CDMP Application. Although we believe that the CDMP can improve the care- and self-management of diabetes, it is necessary and desirable to ensure that the human factors considerations – specifically the interface of the human and the machine/information system – has been fully optimized to make the system easy to use, easy to learn, easy to remember, efficient, and "user friendly". Thus, we have subcontracted AIR to conduct a two-phase human factors study. In phase 1, human factors specialists with extensive experience evaluating medical software and device usability, reviewed the existing CDMP software system. They assessed the software's user interface for consistency of style and navigation aids, the number of keystrokes to perform frequent tasks, the time required to perform these tasks, and potential areas of ambiguity. Also in phase 1, consultants with expertise in diabetes care management will use the CDMP for several hours and provide feedback regarding its ease of use, appearance, logic, accuracy, and ability to facilitate their work flow, among other things. After phase 1 is complete, we will modify the CDMP accordingly and then begin phase 2 of the human factors study. In phase 2, AIR will conduct a usability laboratory study with Joslin Diabetes Center health care providers and patients with diabetes. The participants, after providing informed consent, will use the CDMP to perform tasks simulating actual patient encounters in the ambulatory setting. Participants will be video- and/or audio-taped while using the system, and will be administered a questionnaire afterwards to collect qualitative data regarding subjective impressions. These results will be summarized, analyzed, and aggregated into a report that will make specific recommendations regarding opportunities for improving the system's usability.

Status: The first half of phase 1 is complete. The second half of phase 1 will begin shortly, depending on consultants' availability. We are submitting the protocol for phase 2 to the Joslin IRB. When it is approved, we will submit the protocol to HSRRB for their review.

6. Development and validation of Learning Level Assessment and Readiness to Learn tools for the JVN Telehealth CDMP application

Progress:

These tools have yet to be implemented and have been placed on a low priority by participants in this proposal. It was felt that available tools were cumbersome to use at this point an would see limited utilization by care manager users. The results from these tools would not be used as part of the clinical trials. Once the trials have been initiated then we will address this functionality as part of our value added to the CDMP application

7. Deployment of JVN Telehealth CDMP application in Tripler Army Medical Center and Honolulu VA in Hawaii. D. Peters PhD

This is a deployment activity planned to ensure that these sites come on line with respect to participation in the planned multi-center clinical studies. Based on our experience with deployment of the CDMP application at the Joslin Diabetes Center and at Walter Read Army Medical center, we will have developed a set of standard operating procedures that will facilitate these subsequent deployments of the CDMP application.

Of primary importance is the integration of the application into the existing Health Information System for both the DoD facility and the VA facility at this site. There will be a requirement to perform the appropriate data mapping for integration of related medical record information into the CDMP application. A utility will be developed that automatically updates patient medical record information to the CDMP every 24 hours. There will also need to be a determination of whether or not data collection that is native to the CDMP application also becomes part of the institutional medical record. This will require interface between the IT resources at the site and the IT resources of the JVN team.

The technology requirements are minimal. The site will need to purchase an SQL server with an Oracle license as the CDMP operates off the Oracle database. The site will also need to acquire a Weblogic license as this is the operating system platform for the CDMP. Data communication will be over existing VPN infrastructure.

An evaluation of the site-specific clinical workflow will be performed so as to determine the optimal positioning of the CDMP application within this process.

Once testing of the software integration has been completed a series of training sessions will be scheduled for identified clinical users as well as on site technology people who will provide the first level support on technical issues.

Progress:

The original plan was to have the CDMP reside as an application on the ICDB. The implementation of CHCS II, however, has been accelerated at TAMC and the ICDB is no longer supported. Installation of additional applications at TAMC has been indefinitely postponed until CHCS II has been fully implemented. As a result of these developments, the principal investigators believe that the delay in installation of CDMP and the conduct of the proposed research investigations at TAMC will be unacceptably delayed.

This has resulted in the modification of our proposal to cover the second and subsequent years of contract DAMD17-03-2-0062 that is a competing continuation from the original contract DAMD17-98-2-8017. We are requesting that the implementation of CDMP and associated research studies delineated in the statement of work that were planned at Tripler Army Medical Center (TAMC) in Honolulu, HI be done at alternative sites. The original plan was to have the CDMP reside as an application on the ICDB. The implementation of CHCS II, however, has been accelerated at TAMC and the ICDB is no longer supported. Installation of additional applications at TAMC has been indefinitely postponed until CHCS II has been fully implemented. As a result of these developments, the principal investigators believe that the delay in installation of CDMP and the conduct of the proposed research investigations at TAMC will be unacceptably delayed. The alternative sites proposed are: Waianae Coast Community Health Center, Waianae, HI; The Physicians Center at Mililani, Mililani, HI; and the Molokai General Hospital, Kaunakakai, HI. Preliminary site visits were made by Dr. Deborah Birkmire-Peters, University of Hawaii, Dr. Stephanie Fonda, Joslin Diabetes Center, and Drew Lewis, Estenda Solutions, Inc. to assess the suitability of the sites for the proposed implementation of CDMP and the associated research studies. They determined that each of these sites was appropriate for the proposed research and the staffs indicated enthusiasm for the project. The purpose of this modification to the proposal is thus to transfer the proposed implementation of CDMP and associated research studies delineated in the statement of work that were planned at Tripler Army Medical Center (TAMC) in Honolulu, HI to Waianae Coast Community Health Center, The Physicians Center at Mililani, and the Molokai General Hospital.

8. Deployment of JVN Telehealth CDMP application in VA VISN 1 network. Paul R. Conlin MD

A parallel deployment will be initiated for deployment of CDMP within the VA VISN 1 network. The same issues will be addressed as outline above for deployment in Hawaii.

Progress:

Deployment of CDMP at Joslin Diabetes Center for remote access to the VA VISN 1 network was completed in February 2005. The CDMP will be used to access data for the "Internet Based Diabetes Education and Case Management" study. The protocol has been reviewed and approved by the local VA IRB and is currently under review by the USAMRMC Human Subjects Research Review Board (HSRRB).

9. Deployment of JVN Telehealth CDMP application into the Department of Defense HealtheForces. Robert Vigersky MD, and Sven-Erik Bursell PhD

Progress:

Deployment of CDMP into HealtheForces at Walter Reed Army Medical Center (WRAMC) was completed in May 2005. Diabetes Institute staff at WRAMC received CDMP training in June 2005. The Diabetes Institute staff is currently developing the process and procedures for use of the CDMP in their clinic. Recent requirements regarding interfacing to CHCSII are currently being investigated and a plan has been developed to integrate into CHCS II as discussed below.

10. Establish a centralized JVN Telehealth clinical coordination center to facilitate the proposed multicenter clinical trials. Lloyd M. Aiello and Lloyd P. Aiello, Sven-Erik Bursell. Co-Investigator: Stephanie Fonda, Ph.D.

The JVN Telehealth clinical coordination center is an integral part of JVN program moving forward in the future and will provide the critical capability of providing a variety of professional services that provide value added to the JVN program as it begins to undertake the proposed rigorous multicenter clinical studies. These services will be designed through the clinical coordination center under the direction of Dr. Lloyd M. Aiello and Dr. Bursell and will provide direction and testing of various clinical pathway models as well as coordination and facilitation of different JVN related multi-center clinical trials. The expertise and programs provided through the coordination center will present a compelling value to the JVN participating sites. The immediate tactical services that will need to be sustained through the clinical coordination center are outlined below:

1. Client training on all tools; capture of clinical feedback for software updates; modifications to JVN clinical workflow processes as desired by health professionals using the JVN system.
2. Support for clinical programs development, identifying site-specific program requirements, and clinical pathways and workflows
3. Support for reading center services, establishing and updating certification programs and courses, maintaining performance for image review and reporting services, scheduling timely quality assurance reviews, and providing ongoing consultation services
4. On-going clinical support through resource development, maintaining quality assurance, consultative services, and provision of pre/post-deployment periodic site visits
5. Provide continuing education, both on-site at the JVN Tele-Health Clinical Coordination Center and at remote sites through on site visits or video teleconferencing
6. Coordinate reading centers to provide ongoing certification and re-certification services, for image acquisition specialists, image review specialists, and remote reading centers
7. Coordinate all clinical study activities associated with the clinical coordination center and provide a centralized data repository for the different proposed clinical studies.

Progress:

Development of the Study Manager Module in CDMP with the data base established to support storage of study data and the utilities required to access this data for analysis has been completed and code development for anonymization of data, secure messaging, HIPAA compliance, and centralized storage has been completed.

11. **Clinical validation of the JVN Eye Care computer algorithm for automation of detection of retinal lesions.** Determine the sensitivity and specificity and Receiver Operating Characteristics (ROC) of the performance of the algorithm for detecting retinal abnormalities from undilated eye JVN digital video retinal images compared to dilated eye ophthamological evaluation of retinal images from 35 mm retinal fundus photography.

Progress: The algorithm development has been completed and undergone validation testing. The results of this study will be presented at the Association for Research in Vision and Ophthalmology conference April 24 to 29 2004. Additionally a manuscript has been prepared for submission to SPIEE. This software module will be incorporated in the next JVN version release based on the MS .Net operating system. Algorithm has been reworked with additional improvements to assessment of overall image quality and improved algorithmic detection of retinal features. Currently the new algorithm has undergone training and validation ans is currently being tested against a new set of 216 JVN retinal patient studies. Results from this work have been presented at the ATA meeting in 2005 and at the ARVO meeting 2005. This algorithm will be implemented into the JVN version 3 release at the end of December 2005.

12. **Clinical validation study for the JVN developed retinal imaging device.** Determine the level of agreement in retinopathy diagnosis comparing retinal images taken using the new JVN portable retinal imager and the clinical gold standard of dilated eye ETDRS protocol 35 mm 7 stereo standard field photography.

Progress: This study has not been initiated as retinal prototype development was slowed due to reduction in funding for 2003 and the large gap between completion of prior award and release of funding for this competing continuation. Some additional work has occurred but is a lower priority. Work will occur depending on availability of funds. Currently modifications to the prototype now allow full field retinal images to be acquired without portions of retina being occluded by reflections from the lens and cornea. Currently we are pursuing negotiations with an ophthalmic company to productize the retinal imaging system. Examples of retinal images obtained by this prototype are shown below.

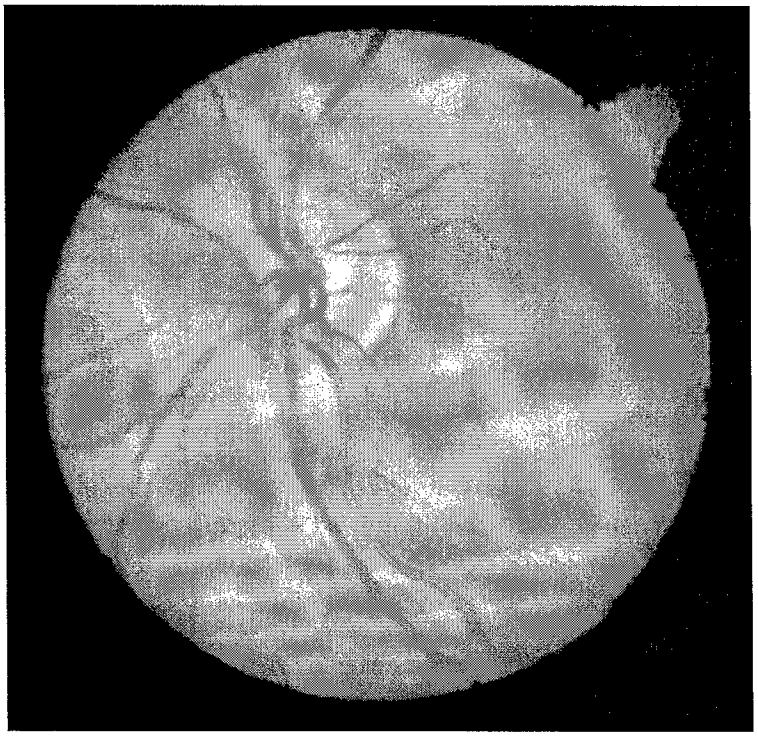


Figure 1: Retinal image obtained from a young normal non-diabetic male volunteer

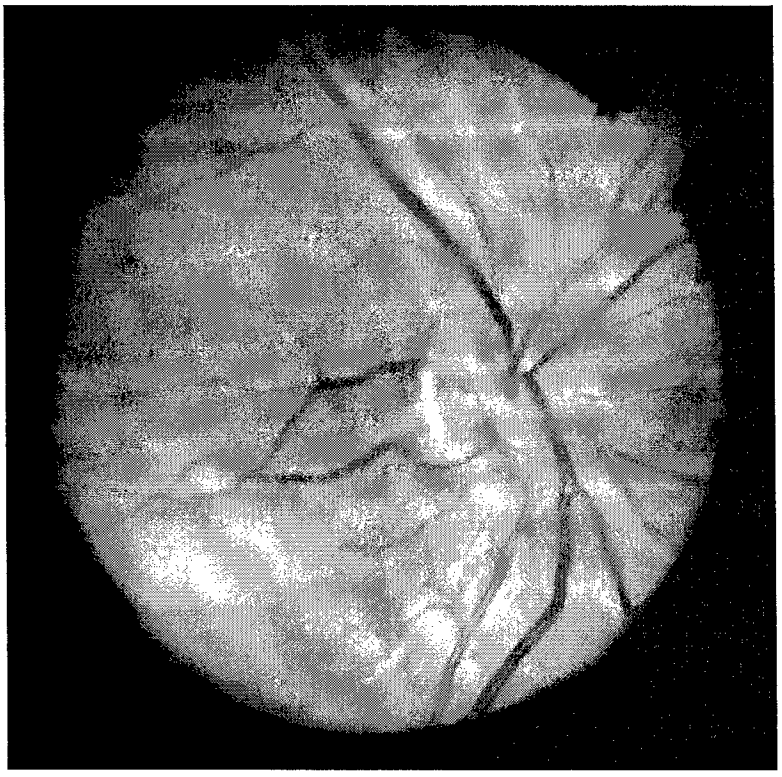


Figure 2. Retinal image obtained from a 60 year old male non-diabetic volunteer

13. **Automation of the retinal image taking process using the JVN developed retinal imaging device.** Development of scanning technology that will automate imaging and simultaneous stereo acquisition of different regions of the retina determined to be essential for accurate diagnosis of diabetic retinopathy.

Progress: This component has not been initiated due to funding reduction in 2003 and the large gap between completion of prior award and release of funding for this competing continuation. Once the retinal imaging device can be produced we will conduct the necessary clinical validation study.

Software Application for 3-Dimensional Visualization of the Retina Optic Nerve Head Mapping from Stereo Pairs

In lieu of the above automation process we have been investigating utilization of image analysis techniques to provide three dimensional mappings of the retina. These would be of value to provide an indication of relative elevation in the macula as an indication of risk for macula edema a sight threatening process or development of optic disc changes potentially associated with the development of glaucoma.

The figures below illustrate the work completed in this area.

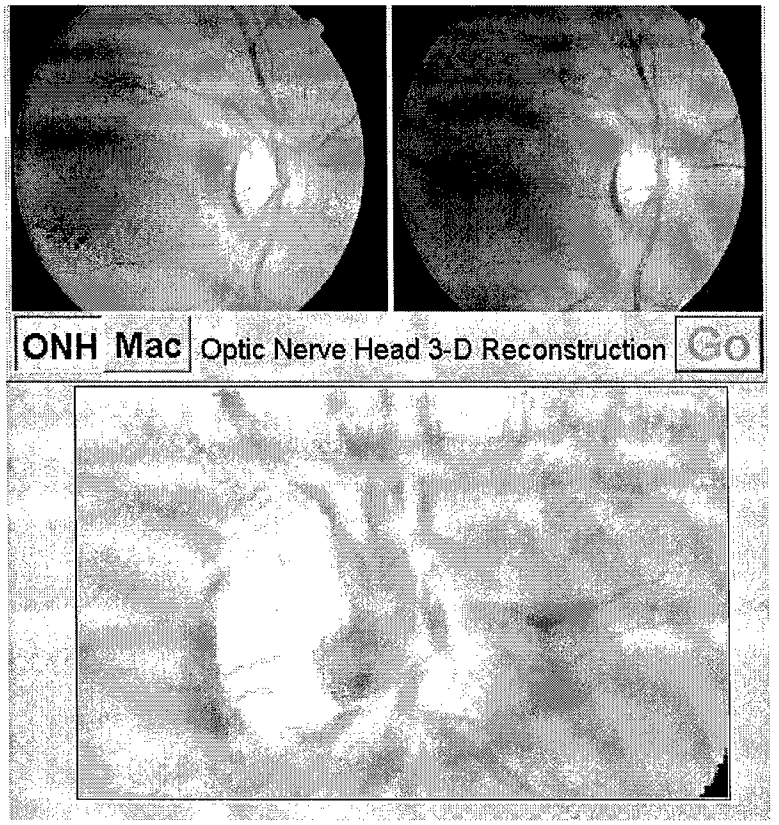


Figure 1. Optic Nerve 3-Dimensional reconstruction for a normal optic disc

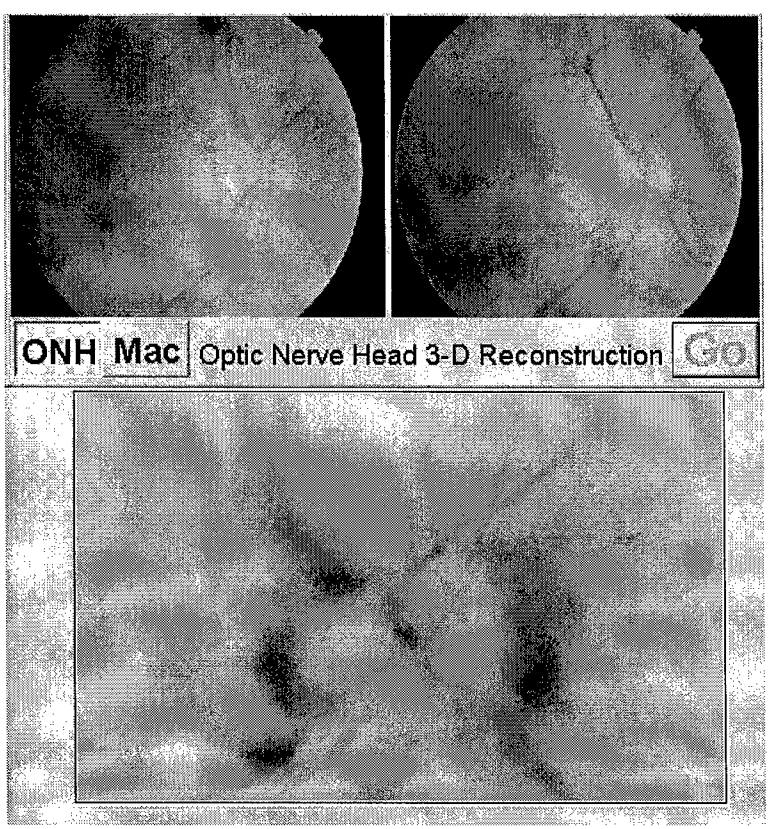


Figure 2. Optic Nerve 3-Dimensional reconstruction for a patient with Papilledema

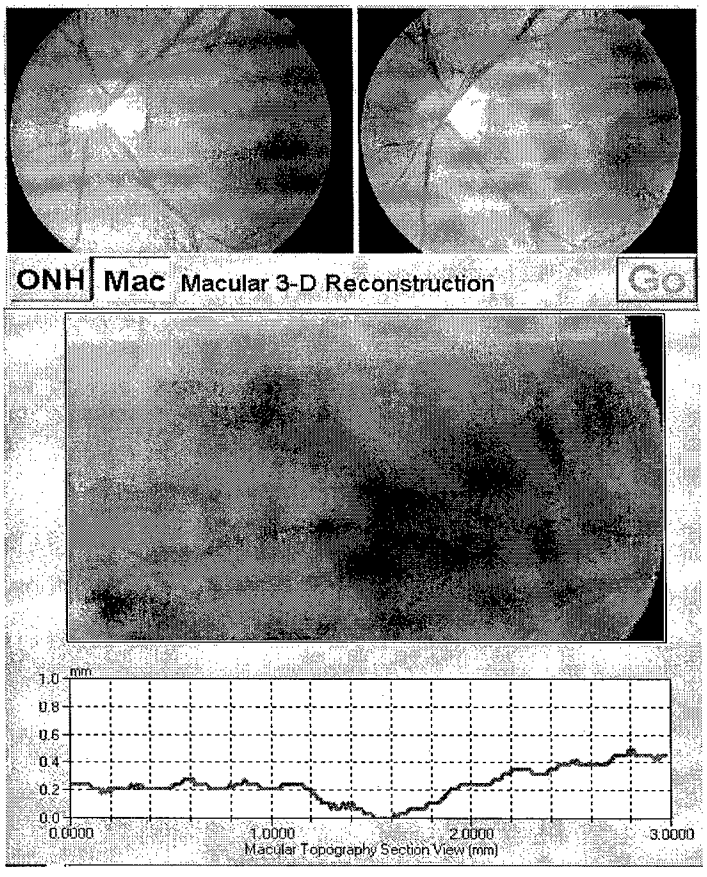


Figure 3. Macula 3-Dimensional reconstruction

14. **Migration of JVN Eye Care module to Microsoft .Net operating platform.** Development of a software enhancement that will allow improvement in performance and reduce costs of technological support.

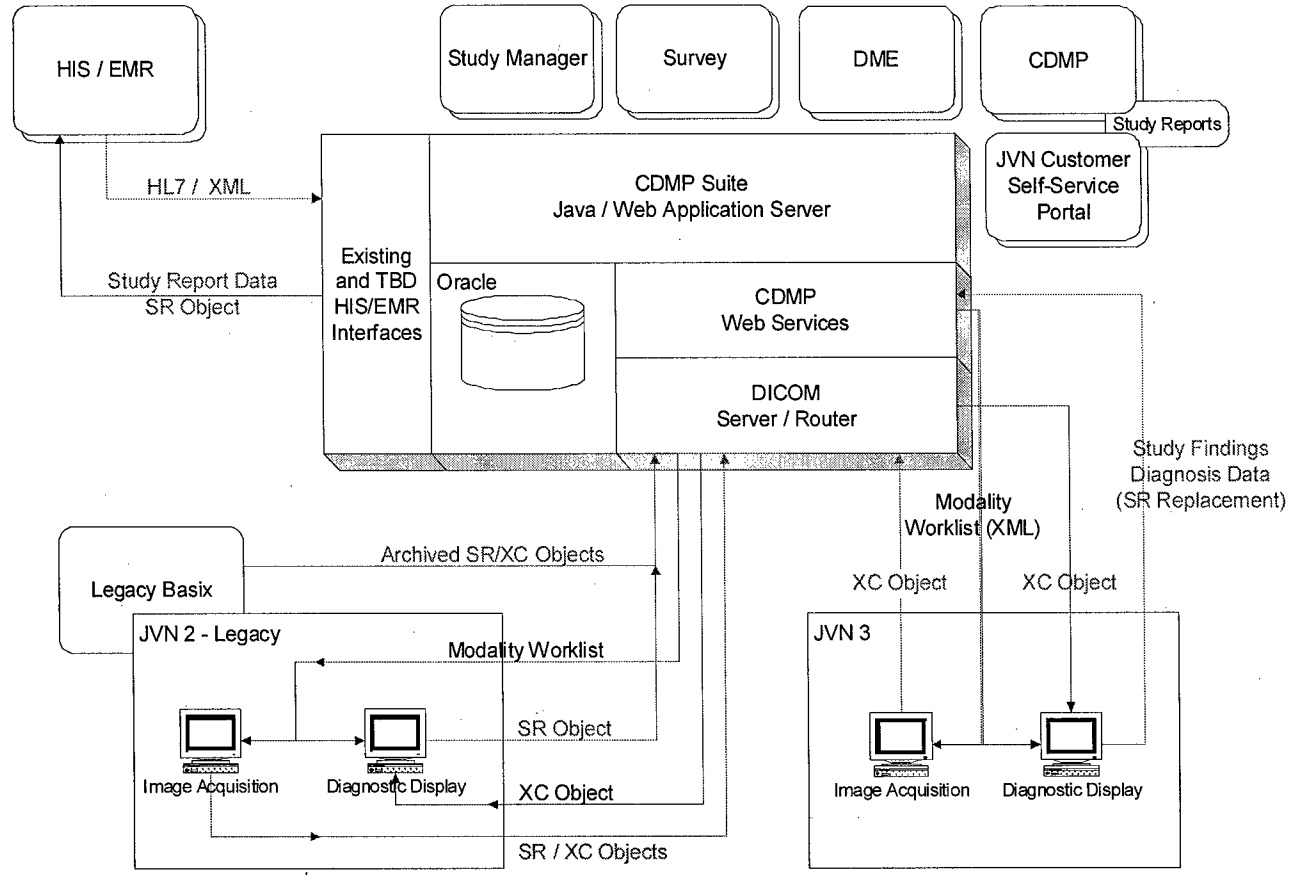
Progress: The software development for the JVN image acquisition application has been completed and is currently undergoing user acceptance testing at the Joslin Diabetes Center. Additional programming needs to be completed for the JVN Diagnostic Display work station that is scheduled for completion in July 2004. In the interim all images captured on the JVN v3.0 software can be viewed on JVN v 2.2 Diagnostic Display workstations. The JVN image acquisition software has been further modified to allow integration of any retinal imaging system into the application. This has required reconfiguration of the acquired images so that they can still be viewed on JVN diagnostic display version 2 work stations.

CHCSII Integration Requirement.

Because of the introduction of CHCS II in the WRAMC Network we have also initiated an effort to accelerate the development of the JVN diagnostic display work station such that the CDMP and JVN eye care are a single application that can be embedded directly into CHCS II. This effort involves the integration of JVN diagnostic display into the CDMP application. It requires the development of a DICOM viewer integrated as a module in CDMP and leverages all the reporting capabilities of CDMP to generate diagnostic findings, clinical, diagnosis and clinical performance reporting. Included in this design will also be the ability to provide assessments and diagnosis for general ophthalmology applications. The advantage here is that the whole application exists on an open architecture leveraging the web based technology used for CDMP and no longer requires reliance on Agfa as a third party vendor for the PACS system. This is a necessity as Agfa has been no responsive to our support requests over the past 18 months despite the fact that we have paid them $30,000 per year for support of our application. The Figure below illustrates the high level architecture for the proposed solution.

We have completed the functional requirements definition portion of the project and currently our in house JVN team and Estenda are working through the technical design portion of the effort. We expect to have available for beta testing amongst the participating study groups by the end of December 2005.

Proposed JVN - CDMP Architecture



In parallel with our in house development effort here we will also work with CHCS II developers to initiate the integration of the JVN application into CHCS II in such a way that the proposed studies at WRAMC are not compromised. The planned work will be accomplished in 3 phases as outlined below:

Phase 1: CDMP entry exists as an icon on the CHCSII web portal. CDMP is still connected to ICDB (Integrated Clinical Data Base) at WRAMC. This will allow us to continue our studies in the short term.
Phase 2: We will establish connection to the CHCSII data repository (CDR) that will take over ICDB function for CHCSII. This provides a more direct connect between CDMP and CHCSII.
Phase 3: Integration of CDMP into CHCSII, establishment of the CHCSII data warehouse by CHCS II development (CDM), removal of CDMP database server with all data now going to CHCSII CDM. At this point we have total integration with CHCS II.

15. **Development of additional modules for the JVN Telehealth CDMP application.** These modules are technology enhancements to the existing CDMP application and will include an outcomes and reporting module, an education scheduling and tracking tool, a knowledge assessment tool, a nutrition module, a patient portal module, integration of wireless home monitoring devices, and a primary care practitioner module.

Progress: Comprehensive Diabetes Management Program (CDMP)

For the last year and a half our we have divided our time - developing new or deepening existing modules, deploying CDMP in a variety of underserved communities, and creating and delivering user help files and training materials.

Overall, we have been able to capitalize on our original mission: Create a patient-centric diabetes treatment application that fills the gaps in standard disease management software and empowers patients to become good self-managers through timely, accurate information and solid, collaborative relationships with their care providers. Support those providers with a number of clinical decision support tools and embedded education.

We are fortunate to be working with our original development team, using a strict system development methodology, conscious of the need for quality and documentation.

New or Updated Features - in reverse chronological order:

- **Reporting Module** - CDMP is establishing a set of standard reports to be embedded and, therefore, available to every user. The first group of reports will fulfill DQIP, HEDIS and other certification criteria. Later reports will encompass more patient, provider, and site performance.
- **Study Manager** - Developed to aid performance reporting and outcomes, this application has generated much interest in the research and provider communities because it lays out the process of capturing that information in a series of successive steps.
- **Nutrition Module** - Bi-level nutrition assessment tools, the first for diabetes generalists to assess patients for the amount of control they have over the food issues in their lives. The second assessment is for CDEs and nutritionists to assess more subtle financial, emotional and lifestyle issues while looking at food choices and control.

  We have begun the process of folding into the module an application that analyzes the selected components of foods and, with a nutrition profile of a patient, evaluates the balance of the patient's meals and makes suggestions that include essential nutrients and foods.

- **Patient Portal** - DME Everywhere, our portal, is evolving with rigorous use by the VA. We have made significant changes in language level and visual clarity in the past six months. The portal allows the patient access to a current CarePlan, health profile with underlying clinical guidelines, and vetted web and other media-based materials for a Learning Plan. The following is a partial list of benefits for the patient:
  - Uploading and trending reports for self-monitoring information - BG, BP and other monitors
  - Self-management advice
  - Wellbeing and coping surveys
  - Lab test results annotated with patient language guidelines
  - Graphical indicators of Vitals - A1c, weight, BP
  - Graphical Health Profile - With risk level (red, yellow, green), assessment taken from Risk Profile along with "How to Lower Risk" *short* narrative in patient-friendly terms
  - Patient Take-Home version of CarePlan - same as the patient is given at a visit
  - Mechanisms to communicate securely with CareTeam on routine issues or problems, such as adjustments to self-management plan, resource information from their care team, non-urgent questions
- **CarePlan** - Significantly updated dynamic care planning is done and adjusted with the patient. The plan addresses our three targets - physical wellness, lifestyle self- management, and psycho-social health - while considering the issues of provider time, data-entry redundancy and plain language. CarePlans are easily updated and created.
- **Survey Architecture** - Our robust architecture has allowed us to add surveys of all types to the core application to assess for depression, willingness to work on problem areas, and education needs.

Training

With a growing user base and more and more requests for demos, we have developed both

- demo systems with scripts that take the user through the core application, DME and the newer assessments and
- training materials that familiarize new users first, with the basic features - Alerts and Reminders, the Patient Snapshot, the Risk Profile, and CarePlanning - then gradually add in nuance and greater detail that optimize the application.

CDMP Clinical Data Warehouse - CDMP was designed to collect and maintain large amounts of data and a structure able to

- de-identify that data,
- perform structured queries,
- provide studies support, and
- develop predictive models.

Expert Reviews

The CDMP and its behavioral survey tool, *Understanding Your Diabetes,* have undergone expert reviews from American Institutes for Research. It is currently undergoing usability tests with the same organization.

Our own semi-annual reviews with the development consortium have produced pragmatic and valuable insights leading to more depth in the tools and greater interest from potential users.

KEY RESEARCH ACCOMPISHMENTS

- Development of study design and protocols for the proposed multicenter clinical studies
- Refinement of the automated retinal image analysis algorithm to improve sensitivity and specificity for detecting microaneurisms
- Retinal imaging prototype is now acquiring good quality retinal images
- Study management module for CDMP completed and ready to be used for start of clinical trials
- CDMP patient portal completed and deployed with CDMP
- Validation of retinal imaging application for detection of non-diabetic retinal findings
- Algorithm development for detecting elevated retinal features has been completed and will undergo clinical testing with comparisons to OCT measurements of retinal thickness

REPORTABLE OUTCOMES

Invited Presentations

2003 Ellerbrock Continuing Education Program, American Academy of Optometry Annual Meeting, Dallas, TX
*Ocular Telemedicine: Challenges and Opportunities

2003 Maine Optometric Association Fall Conference, Dixville Notch, NH
*The Role of Telemedicine in Preserving Vision: Challenges and Clinical Adaptation

2003 OptoEast 2003, Atlantic City, NJ
*The Role of Telemedicine in Preserving Vision" Challenges and Clinical Adaptation

2003 Telemedicine and Advanced Technology Research Center (TATRC) Ocular Telehealth Scientific Workshop, July 8-10.
* Teleophthalmology Outcomes in Diabetic Retinopathy

2003 American Telemedicine Association Annual Meeting, Orlando, FL.
* Chair—Ocular Telehealth Special Interest Group Program: Ocular Telehealth: Focus on Diabetic Retinopathy and Other Applications
* Joslin Vision Network Case Reports

2004 American Telemedicine Association Annual Meeting, Tampa, Florida
*Ocular Telehealth Special Interest Group Short Course Program: Coordinator and Chairperson.
* Joslin Vision Network Ocular Telehealth Programs in a Clinical Setting

2004 NEWENCO Center for Graduate Education. Certificate Program—February 2004
*Diabetes and Tele-Optometry
2005 American Telemedicine Association Annual Meeting: Denver, CO
*Telehealth Practice Recommendations for Diabetic Retinopathy
*Joslin Vision Network: Category 3 Telemedicine for Diabetic Retinopathy
2005 Longwood Medical Ophthalmology Monthly Conference. June 2005.
*Joslin Vision Network Diabetes Eye Care Model: Principles and Applications
2005 Canadian Ophthalmological Society Annual Meeting. Edmonton, Alberta, Canada *American Telemedicine Association Telehealth Practice Recommendations for Diabetic Retinopathy

Original Reports

1. Cavallerano AA, Cavallerano JD, Katalinic P, Tolson AM, Aiello LP, Aiello LM, Joslin Vision Network Clinical Team. Use of Joslin Vision Network digital-video nonmydriatic retinal imaging to assess diabetic retinopathy in a clinical program. Retina 2003; 23:215-223.
2. Wilson C, Horton M, Cavallerano J, Aiello LM. Addition of primary-care based retinal imaging technology to an existing eye care professional referral program increased the rate of surveillance and treatment of diabetic retinopathy. Diabetes Care 2005; 28:318-322.
3. Cavallerano J, Lawrence MG, Zimmer-Galler I, Bauman W, Bursell S, Gardner WK, Horton M, Hildebrand L, Federman J, Canahan L, Kuzmak P, Peters JM, Darkins A, Ahmed J, Aiello LM, Aiello LP, Buck G, Cheng YL, Cunningham D, Goodall E, Hope N, Huang E, Hubbard L, Janczewski M, Lewis JW, Matsuzaki H, McVeigh FL, Motzno J, Parker-Taillon D, Read R, Soliz P, Szirth B, Vigersky RA, Ward T; American Telemedicine Association; Ocular Telehealth Special Interest Group; National Institute of Standards and Technology Working Group. Telehealth Practice Recommendations for Diabetic Retinopathy. Telemedicine Journal and e-Health. 2004;10:469-482.
4. Cavallerano AA, Cavallerano JD, Katalinic P, Blake B, Rynne M, Conlin P, Hock K, Tolson AM, Aiello LP. A telemedicine program for diabetic retinopathy in a Veterans Affairs Medical Center—the Joslin Vision Network Eye Health Care Model. Am J Ophthalmol. 2005:139;597-604.
5. Whited JD, Datta SK, Aiello LM, Aiello LP, Cavallerano JD, Conlin PR, Horton MB, Vigersky RA, Poropatich RK, Challa P, Darkins AW, Bursell SE. A Modeled Economic Analysis of a Digital Teleophthalmology System as used by three Federal Healthcare Agencies for Detecting Proliferative Diabetic Retinopathy. Accepted for Publication Telemed J E Health. 2005
6. Paul R. Conlin, Barry M. Fisch, Anthony A. Cavallerano, Jerry D. Cavallerano, Sven-Erik Bursell, Lloyd M. Aiello. Non-Mydriatic Tele-retinal imaging improves adherence with annual eye examinations in patients with diabetes. Accepted for Publication Journal of Rehabilitation Research and Development. 2005
7. Sing-Pey Chow, Lloyd M. Aiello, Jerry D. Cavallerano, Paula Katalinic, Kristen Hock, Ann Tolson, Rita Kirby, Sven-Erik Bursell, Lloyd Paul Aiello. Detecting Ocular Pathology other than Diabetic Retinopathy in Patients with Diabetes: Comparison of Nonmydriatic Digital Retinal Imaging with Dilated Ophthalmic Examination. Submitted for Publication: Ophthalmology 2005

Reviews/Chapters/Editorials

1. **Cavallerano JD**, Katalinic PL, Strong JD, Cavallerano, AA. Role of telemedicine in preserving vision: Challenges and clinical applications. *Practical Optometry* 2002;13:120-126.
2. **Cavallerano J**, Aiello LM. Emerging trends in ocular telemedicine: the diabetic retinopathy model. *Journal of Telemedicine and Telecare*. 2005; 11:163-166..

Proceedings of Meetings/Abstract and Poster Presentations

1. Coll KJ, Birkmire-Peters D, Katalinic P, Tolson A, Cavallerano A, **Cavallerano J**, Bursell S, Dunlap W, Aiello LM. Joslin Vision Network Impact on Clinical Operations at Tripler Army Medical Center. 2003 American Telemedicine Association Annual Meeting, Orlando, FL.
2. Cavallerano AA, Katalinic P, Cavallerano J, Hock K, Tolson A, DeVita J, Aiello LM, Blake B, Rynne M, Joslin Vision Network Clinical Team. Joslin Vision Network Examination for Diabetic Retinopathy in a Veterans Hospital - Report #3. 2003 American Telemedicine Association Annual Meeting, Orlando, FL.

3. Cavallerano J, Aiello LM, Cavallerano AA, Katalinic P, Bursell SE, Aiello LP, Joslin Vision Network Clinical Team. Joslin Vision Network Imaging without Pupil Dilation for Annual Diabetes Retinal Examination. 2003 American Telemedicine Association Annual Meeting, Orlando, FL.
4. Chow SP, Cavallerano J, Katalinic P, Hock K, Tolson A, Kirby A, Aiello LM, Aiello LP, Bursell S. Comparison of nonmydriatic digital retinal imaging with dilated clinical eye exam for detecting non-diabetes-related pathology in diabetic patients. Poster. 2004 ARVO Annual Meeting. Invest. Ophthalmol. Vis. Sci. 2004 45: E-Abstract 4120.
5. Cavallerano J. American Telemedicine Association Position Statement: Clinical Practice Recommendations for Telehealth for Diabetic Retinopathy. 2004 American Telemedicine Association Annual Meeting: Tampa, FL
6. Coll K-J, Birkmire-Peters D, Pelletier M, Cavallerano J, Bursell S, Dunlap W, Winkle RK, Aiello LM. Joslin Vision Network: Evidence supporting need for comprehensive disease management. 2004 American Telemedicine Association Annual Meeting: Tampa, FL.
7. Chow SP, Cavallerano J, Katalinic P, Hock K, Tolson A, Kirby A, Aiello LM, Aiello LP, Bursell S. Detection of non-diabetes-related pathology in diabetic patients using nonmydriatic digital retinal imaging compared to dilated clinical eye exam. 2005 American Telemedicine Association Annual Meeting: Denver, CO.
8. Hock K, Cavallerano J, Kirby R, Frey L, Tolson A, Aiello LM. Poster. The effect of an adult-diabetes-clinic-based nonmydriatic retinal imaging program on access to diabetes eye care. American Diabetes Association 2005 Annual Meeting. San Diego, CA

CONCLUSIONS

The study design for the proposed multicenter prospective clinical trials have been completed, have received approval though participating organization human subjects review boards and are awaiting final formal approval from HSRRB at USMRMC. These prospective studies are important as they are designed to demonstrate both clinical efficacy and cost effectiveness. If the hypothesis of clinical efficacy and cost effectiveness are born out by the results from these trials then the broad introduction of this application into the health care system will be facilitated and could result in significant health care dollar savings associated with the care of patients with diabetes.

The Comprehensive diabetes management program (CDMP) application has undergone a number of versions and we have developed significant new functionality to the application. We have completed the study management module. This module facilitates the management of any clinical research study using an electronic platform with a centralized study data repository. This will facilitate study management and subsequent data analysis. The time savings on the study management component is expected to be significant and results from the use of this system could be used to demonstrate a broader application of this module for any randomized clinical trial such as a drug study that needs to be performed by a pharmaceutical company.

The other significant effort is the completion of the CDMP patient portal (Diabetes Management Everywhere (DME). The DME portal facilitates secure communication between patient and provider with respect to downloaded patient information such as weight, blood pressure, and blood glucose monitoring values. The system also allows patients to down load digital images for review by care managers, for example patients can down load images of their meals for discussion regarding portion size and calories with nutritionists.

The JVN eye care component is being integrated into the CDMP application. This is significant as we can now leverage the reporting power of CDMP to provide performance reporting and quality assurance. Additionally, the use of the CDMP now means that we no longer need to deploy multiple servers for the JVN application resulting in significant hardware savings as well as support savings. Finally, integration of JVN eye care with the CDMP application allows ultimate embedding of the application into CHCS II and VA Vista systems.

Results fro the JVN eye care studies have shown that the JVN usage for retinal imaging through non dilated pupils is equivalent to both dilated eye photography and a dilated eye exam performed by a retinal specialist (both current clinical gold standards). We have also enhanced the retinal imaging application to include clinical

guidelines based management of eye disease by including systemic risk factors available through the CDMP application.

APPENDICES:

Appendix 1: Presented ARVO 2005

IMPROVED AUTOMATED DIGITAL RETINAL IMAGE ANALYSIS FOR DETECTION OF DIABETIC RETINOPATHY THROUGH IMAGE QUALITY RESTORATION

P. Soliz[1], B Raman[1], SC Nemeth[1], J Barriga[1], G. Zamora[2], and S.E. Bursell[3], [1]ORION International Technologies, Albuquerque, NM, [2]University of New Mexico, Albuquerque, NM, [3]Kestrel Corporation, Albuquerque, NM, [4]Joslin Diabetes Center, Boston MA

OBJECTIVE

Although retinal imaging technology is advancing at a very high rate, it remains impractical and economically infeasible to deploy only the highest available resolution (number of pixels) digital cameras. The purpose of this study was to assess the effectiveness of image "enhancement" techniques on image quality and the subsequent impact on lesion detection and visualization for patients with diabetic retinopathy (DR).

Background

The transition of technology into eye clinics and applications such as telemedicine are constrained by economics, data storage and communications requirements.

Intuitively, better image quality through finer pixel representation of a medical image should improve the sensitivity and specificity with which a physician, human grader or a computer-based algorithm can detect lesions associated with DR.

Decisions to upgrade clinical fundus imagers to "high-end" imaging technologies may unnecessarily add to the healthcare costs, will require additional electronic storage capacity, or additional bandwidth in telemedicine applications. These requirements must be assessed in terms of their value added.

In making these decisions, clinical significance is often not thoroughly evaluated or ignored. This is partially due to the lack of a means for quantitatively evaluating new imaging technologies.

Below is a 2000 by 2000 image pre-processed with two different techniques:

Fig. 1. Original image
Entropy = 6.3, Contrast =16.7

Fig. 2. Histogram equalized
Entropy = 6.9, Contrast = 114.6

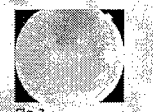


Fig. 3. Spatially-based constrast enhancement
Entropy = 6.3, Contrast = 351.5

Motivation

New or improved imaging technology is needed to increase the sensitivity for detecting disease in retinal images.

One of the most common diagnostics used in the clinic for monitoring treatment or progression of retinal diseases is the fundus image.

Technology to improve image quality at little or no added cost is required for a number of applications in the healthcare system, including remote screening and clinical setting screening and clinical setting.

Higher resolution and greater contrast for improved earlier detection and greater sensitivity.

METHODS

- Joslin Vision Network: 480 by 640, non-mydriatic, stereo images, three fields
  - The low resolution images were 640 by 480 pixels with 45 degree field of view and collected non-mydriatically. Ninety-seven subjects, 74 with no DR and 23 with DR were included.
- The University of Texas Health Science Center, San Antonio, TX: 1000 by 1000
- Apply image illumination correction and contrast enhancement
- Calculate image quality (IQ) metrics to characterize each image
  - Entropy – Spatial Frequency
  - Contrast – etc.
- Evaluate the effects of image processing for contrast enhancement
- Assess image quality effects on automatic lesion detection (microaneurysm segmentation) using Joslin Vision Network images: 480 by 640, non-mydriatic, stereo images with 45 degree field of view and collected non-mydriatically. 97 subjects (74 with no DR and 23 with not DR) were included.

Image Quality Metrics were calculated for image types/modalities:

$$Contrast = \sum_{n=1}^{N_g-1} n^2 \left\{ \sum_{i=1}^{N_g} \sum_{\substack{j=1 \\ |i-j|=n}}^{N_g} p(i,j) \right\} \qquad H = -\sum P(i)\log(P(i))$$

- Sample Images with IQ metrics:

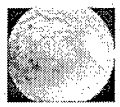


Figure 4. (1543-01) Green channel original.
Entropy = 6.9, Contrast = 10.0
Courtesy of UTSA

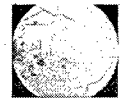


Figure 5. (1543-01) Contrast enhanced.
Entropy = 6.7, Contrast = 12.1

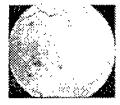


Figure 6. (1543-01) contrast enhanced and edge sharpened.
Entropy = 7.3, Contrast =91.4

Figure 7. (1543-11) Original FA image.
Entropy = 5.8, Contrast =8.6

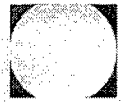


Figure 8. (1543-11) contrast enhanced.
Entropy = 5.7, Contrast =44.8

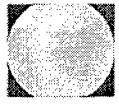


Figure 9. (1543-11) contrast enhanced and edge sharpened.
Entropy = 6.5, Contrast =46.4

METHODS

Computer-based MA Segmentation:

The computer-based digital retinal photo screening system screens low quality images based on image quality metrics prior to the automatic segmentation of MAs.

Uneven lighting is common to most retinal images, especially when illuminated non-mydriatically. An image flattening process is applied to remove the uneven illumination.

The MAs were segmented using a top-hat transformation [2].

Two data sets were used in the study:

The higher resolution images were 1400 by 1200 pixels with 30 degree field of view and collected through pharmacalocially dilated pupils. 10 patients with DR and 8 without DR were included.

Joslin Vision Network images

RESULTS

High resolution fundus images

- A clinical sensitivity of 90% and a specificity of 87.5% were achieved. The dataset is very small and no validation was performed on an independent dataset.

Low resolution fundus images

- A clinical sensitivity of 69% and a specificity of 68% were achieved for the training data.
- A clinical sensitivity of 83% and a specificity of 69% were achieved for the test data.
- Image pre-processing improved sensitivity and specificity to 92% and 74% respectively
- The positive predictive value was found to be greater than the prevalence of both the training and testing sets

Qualitatively and quantatively, the processed images demonstrated removal of illumination artifacts and help the analyst to better visualize lesions, especially in underexposed regions of the image.

CONCLUSION

This project demonstrated that image quality through image enhancement techniques can add significantly to the detection of lesions through automated means or in the visualization by readers.

Acknowledgments: Funding for this study were provided in part from a contract sponsored by the Department of the Army through Cooperative Agreement DAMD 17-3-02-0062 for the Joslin Department of Defense (DOD)/Department of Veterans Affairs Program. The content of the information within this program does not necessarily reflect the position or the policy of the government, and no official endorsement should beinferred. Data were also provided by Dr. Tom Fitzsimmons from the University of Texas Health Science Center, San Antonio TX. The MA segmentation research was performed by PS and BR while employed by Kestrel Corporation, Albuquerque, NM. Our thanks to Mr. Gene Butler (President/CEO of Kestrel) for allowing us to present those results.

Appendix 2: Presented ATA 2005

THE EFFECT OF IMAGE QUALITY ON MANUAL AND COMPUTER-BASED SCREENING FOR DIABETIC RETINOPATHY

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OBJECTIVE

To assess the impact of image quality on the effectiveness of detecting diabetic retinopathy (DR) lesions in retinal images.

Background

Today's telemedicine systems are constrained by economics and communications capabilities.

Intuitively, better image quality through finer pixel representation of a medical image should improve the sensitivity and specificity with which a human greater or a computer-based algorithm can detect lesions associated with DR.

Decisions to upgrade to "high-end" imaging technologies that may unnec unnecessarily add to the cost of the medical service and will require additional bandwidth must be assessed in terms of their value added.

Clinical significanca is often not thoroughly evaluated or ignored.

Fig. 1. 480 x 640 pixels

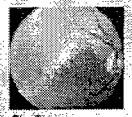

Fig. 2. 1K x 1k pixels

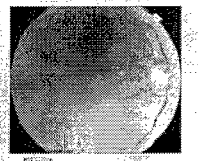

Fig. 3. 2K x 2k pixels

Motivation

New or improved imaging technology is needed to increase the sensitivity for detecting disease in retinal images.

One of the most common diagnostics used in the clinic for monitoring treatment or progression of retinal diseases is the fundus image.

Technology to improve image quality at little or no added cost is required for a number applications in the healthcare system, including remote screening and clinical setting screening and clinical setting.

Higher resolution and contrast for improved earlier detection and greater sensitivity.

METHODS

Data from three different fundus cameras were provided by:

- Joslin Vision Network: 480 by 640, non-mydriatic, stereo images, three fields
  - The low resolution images were 640 by 480 pixels with 45 degree field of view and collected non-mydriatically. Ninety-seven subjects, 74 with no DR and 23 with DR were included.
- The University of Texas Health Science Center, San Antonio, TX: 1000 by 1000
- The University of Texas Medical Branch, Galveston, TX: 2000 by 2000,
- Apply image quality (IQ) metrics to characterize each image
  - Entropy
  - Contrast
  - Spatial Frequency
  - etc.
- Develop a preliminary, qualitative model that correlates visual perception of IQ with these metrics
- Evaluate the effects of image processing for contrast enhancement
- Apply automatic lesion detection (microaneurysm segmentation)

Image Quality Metrics were calculated for image types/modalities:

$$Contrast = \sum_{i} n^{2} \sum_{|i-j|=n} \sum p(i,j) \qquad H = -\sum P(i)\log(P(i))$$

- **Sample Images with IQ metrics:**

Figure 4. (1543) Green channel. Entropy - 6.7, Contrast - 12.1, Spatial Frequency - 4.1

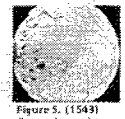

Figure 5. (1543) Green channel. Contrast enhanced Entropy - 7.2, Contrast - 112.7, Spatial Frequency - 11.0

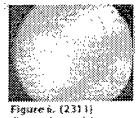

Figure 6. (2311) Green channel. Entropy - 5.1, Contrast - 33.8, Spatial Frequency - 4.0

Figure 7. (1777-9) Green channel. Entropy - 5.2, Contrast - 10.4, Spatial Frequency - 4.5

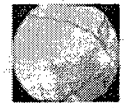

Figure 8. (1777-01) Green channel. Entropy - 6.1, Contrast - 9.3, Spatial Frequency - 3.7

Figure 9. (2286) Green channel. Entropy - 6.2, Contrast - 33.8, Spatial Frequency - 7.6

RESULTS

High resolution fundus images

- A clinical sensitivity of 90% and a specificity of 87.5% were achieved. The dataset is very small and no validation was performed on an independent dataset.

Low resolution fundus images

- A clinical sensitivity of 83% and a specificity of 69% were achieved for the training data.
- A clinical sensitivity of 83% and a specificity of 69% were achieved for the test data.
- Image preprocessors improved sensitivity and specificity to 92% and 74% respectively
- The positive predictive value was found to be greater than the prevalence for both the trainint and testing sets

CONCLUSION

This project demonstrated that image quality through image enhancement techniques can add significantly to the sensitivity and specificity of screening for DR in at risk patients without increase bandwidth requirements, and with little added cost.

Acknowledgments: Funding for this study were provided in part from a contract sponsored by the Department of the Army through Cooperative Agreement DAMD 17-1-02-0062 for the Joslin Department of Defense (DOD)/Department of Veterans Affairs Program. The content of the information within this program does not necessarily reflect the position or the policy of the government, and no official endorsement should be inferred. Data were also provided by Dr. Tom Fitzsimmons and Dr. Helen Lieon the University of Texas Health Science Center, San Antonio TX and the University of Texas Medical Branch, Galvestor, TX. The research was performed by PS and BR while employed at Kestrel Corporation, Albuquerque, NM. Our thanks to Mr. Gene Butler (President/CEO of Kestrel) for supporting the research represented in this material.

Appendix 3.

Submitted for Publication:

The Effects of Spatial Resolution on an Automated Diabetic Retinopathy Screening System's Performance in Detecting Microaneurysms for Diabetic Retinopathy

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Abstract

This paper presents the effects of image quality, given by the number of pixels used to define the image. A microaneurysm (MA) segmentation algorithm that has been shown to achieve about 90% sensitivity and specificity for clinical classification using high resolution images of those diabetic patients who present with MAs was applied to low resolution images to assess the effects of lower resolution of sensitivity and specificity. The low resolution (640 by 480 pixels) 45° field of view (FOV) was provided by a non-mydriatic camera. High resolutions images from a mydriatic fundus camera were acquired by digitizing 35mm color film slides to 1400 x 1200 pixels for a 30° FOV. The image quality of the digitized 35mm images was considerably better than those from the non-mydriatic camera. Segmentation of microaneurysms (MAs) was performed using the green channel image of the two modalities. The images were contrast enhanced and corrected for uneven illumination. The images were then filtered using a tophat morphological filter and a threshold applied to segment the candidate MAs. Because the retinal vessels are similar in intensity and contrast to MAs, the retinal vasculature was segmented using matched filters to remove the vessel artifacts from the image. Ground truth, which was provided by an ophthalmic analyst, was used in the tuning step to find the bounds of the different intensity and shape features that characterize the MAs. These features were used to distinguish between MAs from other artifactual objects on the image. The best result that could be achieved with the lower resolution images was 70% sensitivity and specificity. We have found that the effects of pixel resolution on an automated segmentation routine to be of significant in obtaining higher sensitivity and specificity.

1. Significance

Diabetes has reached epidemic levels in the developed countries. Retinopathy is one of the most common complications of diabetes, which if not managed appropriately can lead to vision loss and blindness. There is a need for early diagnosis and appropriate management and treatment of diabetic retinopathy and macula edema by retinopathy assessment in the diabetic population at regular intervals as recommended through standard practice guidelines. In present health care systems, screening of retinal images for diabetic retinopathy is limited by its extensive need for human resources. An automated computer based system for base line retinopathy assessmentwill aid in reducing the future economic impact on health care professionals and ensuring proper treatment for those patients where timely diagnosis could prevent blindness.

2. Related Work

A number of research efforts in screening patients for diabetic retinopathy using automatic segmentation of MAs have been previously reported. Larsen et al. (2003) [9, 10], evaluated the performance of an automated fundus photographic image analysis algorithm in high-sensitivity and/or high specificity classification of patients with diabetes with undiagnosed DR from those without retinopathy. In their study, the data set consisted of 260 diabetic patients of which 137 presented with DR. The images were taken with a 60 degree FOV mydriatic camera centered on the macula and the image size was 1947x1296 after digitization of the 35mm slides. When adjusted to high sensitivity, the automated system demonstrated sensitivity at 0.93 and specificity at 0.72. When adjusted to high specificity the automated system demonstrated a sensitivity of 0.76 and specificity at 0.97. Their approach limited significantly the regions of interest that were processed for retinopathy screening. Their paper did not describe the issue of image quality, i.e. how the images that were processed were selected. In addition to image quality, other criteria such as patient selection and regions of interest were not described.

Spencer et al. (1996) [3], described an image processing strategy for the segmentation and quantification of MAs in fluorescein angiograms (FAs) of the ocular fundus. A total of only 4 images with many micro-aneurysms (>20 per image) were used for the validation. A maximum value of 0.82 sensitivity was achieved by the computer's segmentation with approximately 250 false positive MAs detected in all 4 images. Since the true negatives are undefined, the specificity cannot be calculated. The most significant observation of their study in relation to this study is their use of fluorescein angiograph images. FA images are significantly higher contrast and are therefore would expect to achieve higher sensitivity in detecting and segmenting MAs.

Yang et al. (2001) [2], described an algorithm for detecting MAs in low resolution (20 microns per pixel) color fundus images. The algorithm is specifically designed for low-resolution images in order that it may be used in low-cost ophthalmic imaging systems for mass screening program. Using images from three normal retinas, Yang et al. inserted hundreds of artificial MAs into the images to produce a ground truth for measuring the performance of their algorithms. Unfortunately, the size distribution and contrast of these artificial MAs was not given. Yang et al. tested the algorithm on 46 images from a Canon non-mydriatic color fundus camera (of normal and diabetic patients) and achieved a global clinical sensitivity of 0.90 (the ability to detect at least one MA in an eye with diabetic retinopathy) and 0.80 global clinical specificity (the ability of not detecting any MAs in a healthy eye). Though the results reported are better than ours, they used a smaller data set from a single field to evaluate their performance and detailed results were not reported. Further, the ROC curve in their study shows a very high rate of false positives at 90% sensitivity. Again, there is no description on how the subjects for the image set were selected. A bias can be introduced by not selecting subjects randomly to reflect the spectrum of image quality as affected by an individual's pupil diameter, clarity of the anterior segment, and pigmentation.

Philips et al. [1] reported on quantification of diabetic maculopathy by digital imaging of the fundus. They used FAs to segment and count MAs. A system called ADRIS [12] (an automatic diabetic retinal image screening system) was cited in the literature and was used to screen patients for eye diseases where the focus was on optic cup to disc ratio, presence of exudates and tortuous blood vessels.

The literature review supports a number of conclusions:

1. Improved sensitivity and specificity are correlated to the resolution of the digital images [9].
2. Performance of computer-aided screening of digital images improves when pupil dilation is used in the photography [9].
3. There is no published evidence that a robust computer-aided screening system for diabetic retinopathy exists.
4. Published studies have not explained how to manage multiple fields in determining the clinical classification of DR for an eye.

3. Dataset

Two different data sets were used to test the screening system. Low resolution images were collected using a 45° FOV (640x480) stereo non-mydriatic digital video color camera (Topcon TRC NW-5S, Paramus, NJ). The data was provided by the Joslin Diabetes Center and are described by Bursell, et al. [4]. Three different fields; one centered on the macula, one on the superior temporal region and one on nasal were captured for each patient [4]. Training was performed on retinal images from 97 subjects (74 with No Diabetic Retinopathy (NDR) and 23 with diabetic Retinopathy (DR)). A validation was performed on an independent data set (non-mydriatic) of 91 subjects (56 NDR and 35 DR). Images of this dataset were screened by an algorithm that used Fourier power spectral density as a metric for image quality. High resolution images were collected from 35mm color images with a 30° FOV through dilated eyes with a standard fundus camera. A total of 18 subjects (10 DR and 8 NDR) were used in this study. Images of this dataset were selected by an expert retinal grader.

4. Methods

The computer-based digital retinal photo screening system first identifies automatically those digital fundus images of sufficient quality for the automatic segmentation of MAs by calculating the Fourier power spectral density. Those photographs that do not meet a minimum image quality standard are referred to the human grader for manual reading. The images that passed the quality test were then corrected for non-uniform illumination using a Gaussian filter [5]. Applying the Gaussian filter to an image results in a low-pass filtered image that represents the global lighting distribution. This low-pass filtered image is subtracted from the original image to produce an image that appears to be more evenly illuminated. Uneven lighting is common to most retinal images, especially when illuminated non-mydriatically.

The MAs were segmented using a top-hat transformation [3]. The segmented image was then binarized. Segmentation of the retinal vessels was performed using a Gaussian-matched filter [6, 7]. The resulting retinal vessel image was used as a mask to remove noise in the MA-segmented image that was due to retinal vessel residue from the top-hat transformation intended to segment only the MAs. The top hat transformation can and usually does segment a number of objects that are not MAs, *i.e.* false positives. The number of false positives is minimized by classifying the objects according to features (such as shape and color) that discriminate MAs from the general assortment of false positive objects. The optimal range of values for features that represent MAs were found using a search algorithm where the goal was to maximize the number of true positives (objects that are MAs) and minimize the false positives (objects that are not MAs) as manually defined by an ophthalmic technician (grader).

Since there are low resolution images for three fields for each patient, the information (segmented objects) from the three fields was combined to yield the clinical classification (normal or DR). Each segmented image contained objects there were classified by the analyst as true positives, but there remained a certain number of false positive objects. Our approach for producing a clinical diagnosis was based on the statistical probability that the number of objects in a segmented image that were true positives would increase as the total number of segmented objects increased. Additionally, it was believed that the statistical distribution of true positives and false negatives varied from field to field. A genetic algorithm [8] was used to determine the optimal weighting to apply to the objects in each of the three fields and to discover an optimal threshold that yields the greatest clinical sensitivity and specificity.

This final step in the screening process makes this system differ from those previously developed and cited in the literature [9, 10]. The screening system implemented a technique that made it unnecessary to detect automatically all MAs and to reject all other segmented objects that resemble MAs in an image. To screen the segmented digital images, a threshold for objects (true positives and false positives) was determined statistically using a database of retrospectively analyzed data, such that a digital image presenting with objects greater than a critical threshold is classified as one coming from a patient with diabetic retinopathy. Figure 1 illustrates this concept where images having a number of segmented objects greater than the critical threshold (8 objects) are classified as a patient with diabetic retinopathy. In this illustration an image with 6 to 11 segmented objects can be either normal or diabetic retinopathy. There is a trade-space that determines the sensitivity and specificity depending on the selection of the critical threshold. A receiver operating characteristic (ROC) curve is constructed by varying the threshold, allowing the user to select a desired screening sensitivity and specificity. In this approach, the process does not attempt to maximize the clinical sensitivity based on detecting all or most of the MAs in any of the given fields, but rather optimizes the clinical sensitivity and specificity by using statistical information on the number of objects that are segmented.

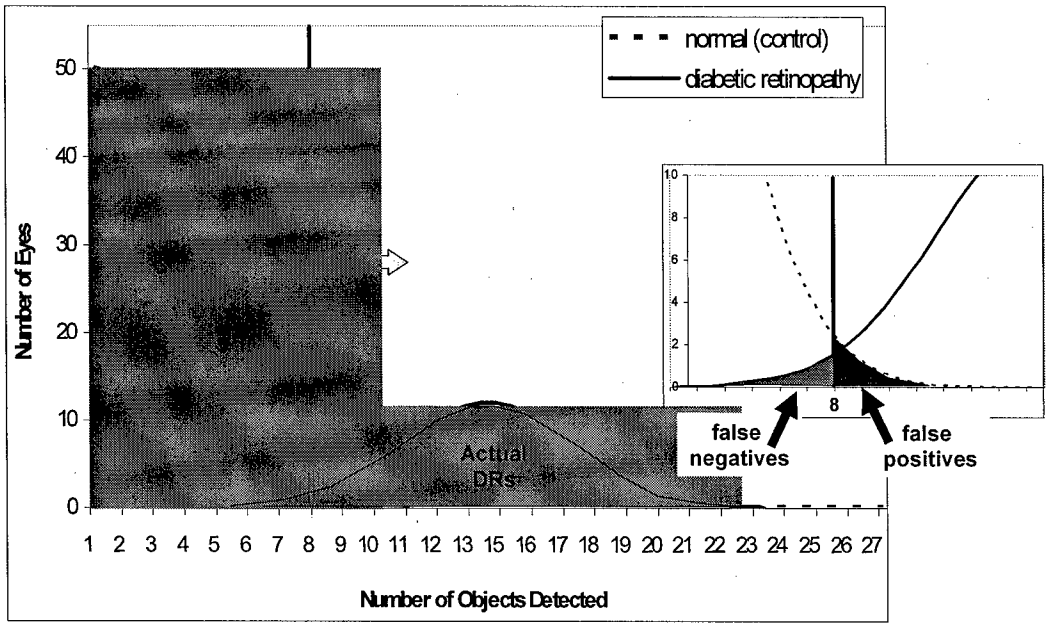

Figure 1. Illustration of how a threshold for the number of objects detected determines the true and false positive and true and false negative rates. For the threshold ≤ 8, those eyes with less than or equal to 8 objects would be classified as normal; however, the distribution of diabetic retinopathy eyes with 6 to 8 objects is not zero. Those eyes could be miss-classified as normal. Conversely, there are a few cases where normal eyes have 9 to 10 objects. Those eyes would be mis-classified as diabetic retinopathy, but could actually be normal.

5. Results

5.1. High Resolution Fundus Images

The results presented here are from a training dataset that included 10 abnormal and 8 normal subjects with only one field. A clinical sensitivity of 90% and a specificity of 87.5% were achieved with a threshold of 6 objects. Figure 2 gives the results on segmentation from high resolution images. Though the dataset is very small and no validation was performed with an independent dataset, we could segment more MA's and minimize the number of FP's significantly on the normal images and achieve a high clinical sensitivity and specificity.

5.2. Low Resolution Fundus Images

Our goal was to determine the maximum clinical sensitivity and specificity that is achievable for the low resolution fundus images. For the training set, we achieved a clinical sensitivity of 83% and a specificity of 69%. For the independent validation set, we achieved a clinical sensitivity of 69% and a specificity of 66% with a weighted threshold of 2 objects by combining all three fields. The prevalence of normal and abnormal patients in training is 0.24 and 0.76 respectively. The prevalence of normal and abnormal patients in validation is 0.39 and 0.62 respectively. The positive predictive value and the negative predictive value were found to be greater than the prevalence for normal and abnormal in both training and validation. This shows that the algorithms is always better than chance in detecting abnormal/normal patients

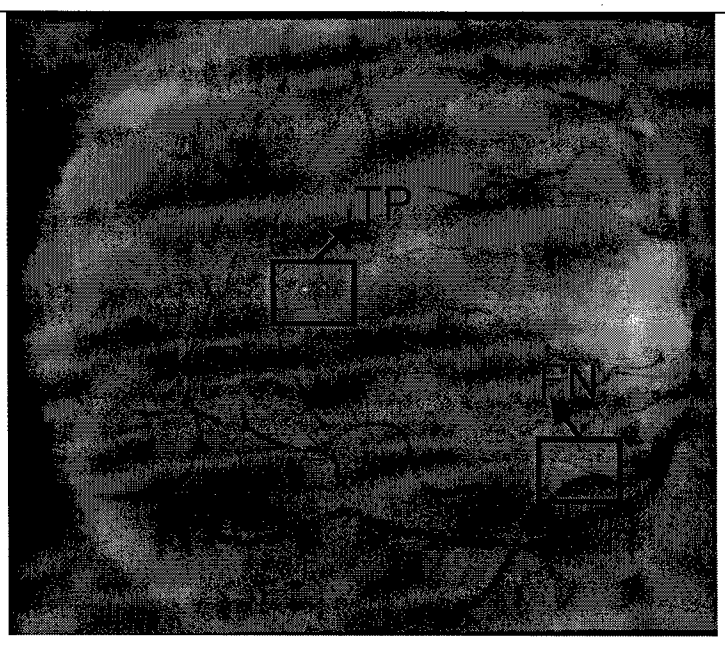

Figure 2. MA segmentation of high resolution images. The true positives and false negatives were identified on the image. There are no false positives segmented on this image.

Conclusion

There are medical and technical reasons why one would prefer to have low resolution images collected on non-mydriatic cameras for broad scale screening of the at-risk population. From a medical perspective, a non-mydriatic fundus camera would allow retinal imaging without the need for dilating eye drops (Lower light levels for imaging ease of use for imagers, and improved patient compliance). However, the non-mydriatic fundus camera produces images with less contrast and poorer over all lighting than the mydriatic camera where the subjects' eyes have been dilated. There are technical motivations for lower resolution images. For telemedicine applications, transmission and storage of large images can result in bottleneck in the system. Implementers of tele-health systems want to keep the bandwidth requirements for transmitting data as low as possible to reduce costs.

Our study has shown that reduced image quality, including lower resolution, will result in lower sensitivity and specificity in the clinical classification of patients with MAs. The study showed only two extreme image quality levels. In the future, a study is needed that shows whether the loss of sensitivity and specificity is linear or non-linear in progressing from 90% to 70%. One would like to know what aspects of image quality are the most important, e.g. contrast or resolution. Image compression may also need to be studied in terms of its effect on sensitivity and specificity.

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